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Poor clinical outcomes in respiratory viral sepsis: a retrospective observational study

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Ethics statement: The institutional review board of the China–Japan Friendship Hospital approved this study (2023-KY-011).

ABSTRACT

Objectives: This study attempts to explore the clinical differences of sepsis caused by respiratory viruses and bacteria, and to search for risk factors for mortality in viral sepsis.

Methods: This single-center, retrospective cohort study enrolled patients hospitalized at our medical intensive care unit (ICU) from October 2020 to January 2024 who were diagnosed with pneumonia and sepsis. The primary and secondary pathogens were identified with comprehensive etiological tests. The baseline clinical information, biochemical tests, treatments, and clinical outcomes were collected.

Results: This study included 292 patients, comprising 191 with viral sepsis and 101 with bacterial sepsis. Compared with the bacterial sepsis group, patients with respiratory viral sepsis had lower oxygenation index levels upon ICU admission, higher proportions of acute respiratory distress syndrome (85% vs 44%, $p<0.001$), secondary infection (84% vs 39%, $p<0.001$), and higher ICU mortality (57% vs 43%, $p=0.018$). After adjustment, viral sepsis patients had an odds ratio of 2.26 (95% CI, 1.26–4.07) for ICU mortality. Risk factors for ICU mortality in viral sepsis included age, sequential organ failure assessment score, secondary infection, immunocompromised status, and coronary heart disease. The subgroup analysis showed that secondary infection in viral sepsis contributed to a poorer clinical outcome.

Conclusion: ICU patients with respiratory viral sepsis presented a higher incidence of unfavorable outcome, which may partially be attributed to secondary infections.

Keywords: viral sepsis, bacterial sepsis, mortality, secondary infection, risk factors.

Introduction

Sepsis has been identified as one of the leading causes of mortality in patients admitted to intensive care unit (ICU) [1]. Classical sepsis is known to be the consequence of bacterial infections, and immediate broad-spectrum antibiotics are strongly recommended for patients presenting with sepsis or septic shock [2]. However, viruses may also serve as the causative pathogen for sepsis, yet they have not received sufficient attention. The reported proportions of bacteria among patients with sepsis were around 40%, while the respiratory viral infection was supposed to be underdiagnosed in previous research [3]. Respiratory viruses, including influenza A and B, respiratory syncytial virus, human metapneumovirus, adenovirus, and coronavirus, were identified in approximately one-third of adult septic patients and had the potential to cause severe disease [3]. Thus, viral sepsis has been defined as life-threatening organ dysfunction resulting from a dysregulated host response to viral infection [4].

The pathophysiology of sepsis includes dysregulated immune response against an invading pathogen, and thus resulting in a condition characterised by sustained excessive inflammation and immune suppression. The excessive inflammation, mediated through increased release of pro-inflammatory cytokines, referred to as the 'cytokine storm' in the case of SARS-CoV-2 associated sepsis, whereas in bacterial sepsis is labeled as the systemic inflammatory response syndrome. The state of immune suppression in patients with bacterial sepsis, which often presents after the excessive inflammation, may occur at an earlier stage in SARS-CoV-2 associated sepsis [3]. The immune suppression results from the apoptotic depletion and exhaustion of immune

cells [5]. This might lead to an increased susceptibility for secondary infections and further contribute to higher mortality in later phase of sepsis.

Since the global outbreak of COVID-19, viral sepsis resulting from respiratory virus infection has been brought back into the attention of numerous researchers, and considerable efforts have been devoted to comprehend the novel concept 'respiratory viral sepsis' [3, 6]. Recently, limited studies have compared the clinical characteristics and outcomes between bacterial and COVID-19 associated sepsis, and have yielded seemingly inconsistent results [7-9]. These studies shared similar limitations, which lie in the fact that only SARS-CoV-2 was included as the pathogen for viral sepsis, coupled with a relatively small sample size and a lack of introduction to the methods of etiological detection. Moreover, the lack of secondary infection analysis was a major limitation since secondary infections have been demonstrated to significantly exacerbate the clinical course and deteriorate the prognosis, particularly among ICU patients.

Therefore, a more comprehensive comparison about the difference between a broad spectrum of respiratory viruses and bacteria associated sepsis is indeed of great significance to a better understanding of the pathogenesis of sepsis, thereby contributing to clinical practice. The aim of this study was to investigate the difference in baseline characteristics, laboratory tests, clinical management strategies, and various clinical outcomes between bacterial and respiratory viral sepsis in ICU patients. Additionally, we sought to establish the role of secondary infection in worsening the prognosis of sepsis.

Methods

Study design and population

This retrospective, observational study was conducted in the ICU of a tertiary center between October 2020 and January 2024. The institutional review board of the China–Japan Friendship Hospital approved this study with a waiver of informed consent due to the retrospective and non-interventional design (2023-KY-011). This research was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975. The inclusion criteria for patients with sepsis encompassed individuals aged over18 years, with pneumonia as the primary diagnosis, admission to ICU, and definite clinical outcomes (either discharge alive or deceased) confirmed in the medical records. Both immunocompromised and immunocompetent patients are eligible. Patients were excluded if one of the following criteria was met: 1) the primary pathogen leading to sepsis cannot be determined due to a lack of identified pathogen or coinfection with multiple pathogens detected simultaneously; 2) noninfectious diseases such as acute cerebral hemorrhage necessitating invasive mechanical ventilation (IMV) and subsequently resulted in ventilator-associated pneumonia; 3) pneumonia secondary to perioperative infections following lung transplantation or pulmonary lobectomy; 4) chronic respiratory failure requiring long-term oxygen therapy; 5) concomitant tuberculosis or HIV infection; 6) primary infection with mycoplasma, chlamydia, or fungi.

Data collection and definitions

Data regarding patients' demographics, comorbidities, biochemical and etiological tests,

treatments, and outcomes were collected from medical records using the Research Electronic Data Capture platform. The combination antibiotic therapy is defined as the use of at least two different kinds of antibiotics. Besides, the worst value of lactate acid and oxygenation index examined at the onset of sepsis, within 48 hours after hospitalization and ICU admission were collected. The worst Sequential Organ Failure Assessment (SOFA) score and Pneumonia Severity Index (PSI) score were calculated upon ICU admission. Sepsis was defined as the presence of infection accompanied by an increase of ≥2 points in SOFA score based on Sepsis-3.0 criteria [2]. Viral sepsis was defined as sepsis resulted from viral pneumonia. Septic shock was defined as sepsis with sustained hypotension requiring vasopressors together with having a lactate level >2 mmol/L despite sufficient resuscitation. Diagnosis of bacterial and viral infection was established based on a comprehensive set of etiological tests, encompassing pathogen culture, polymerase chain reaction (PCR) assays, antigen tests, and metagenomic next-generation sequencing (mNGS). A positive test result, consistent with clinical symptoms, imaging findings, laboratory examinations, and therapeutic response, will serve as the definitive basis for the diagnosis. Respiratory secondary infection was diagnosed when patients presented with compatible clinical symptoms, accompanied by a positive laboratory-confirmed aetiological result, occurring more than 48 hours following the initial diagnosis of primary infection. A viral pathogen was considered positive if a virus was detected in bronchoalveolar lavage fluid (BALF) using real-time PCR or mNGS, or in nasopharyngeal swabs using real-time PCR. A bacterial pathogen was considered positive if any of the following

criteria were met: 1) a positive bacterial culture from blood or BALF; 2) a positive urinary antigen test for *Legionella. pneumophila* or *Streptococcus. pneumoniae*; 3) detection of *L. pneumophila* in sputum or BALF using real-time PCR; 4) a positive bacterial test in BALF using mNGS; or 5) bacteria with moderate to heavy growth (graded as >3+ growth) in qualified sputum or endotracheal aspirate, or a quantified culture in BALF of ⩾10^4 CFU·mL−1. Qualified samples were defined as those containing more than 25 leukocytes and less than 10 epithelial cells per magnified field (at ×100 magnification). Further details can be found in previous research [10-12].

Furthermore, overweight was defined as Body Mass Index >25 [13]. ICU admission was based on the diagnosis of severe pneumonia, which, along with acute respiratory distress syndrome (ARDS), followed the latest guidelines [14, 15]. Immunocompromised status was defined by the presence of underlying diseases including hematological malignancies, active solid tumors, solid-organ transplantation, as well as long-term or high-dose administration of corticosteroids or immunosuppressants [16].

The primary outcome was ICU mortality, and the secondary outcomes included the occurrence of secondary infection, ARDS, septic shock, acute kidney injury (AKI), length of hospital stay, and clinical interventions such as receiving IMV, extracorporeal membrane oxygenation (ECMO).

Statistical analysis

Continuous variables were described as median (interquartile range, 25%-75%) or mean and standard deviation based on the presence of normality of distribution tested

by the Kolmogorov-Smirnov test, and categorical data were expressed as numbers and percentage. Continuous data were analysed using a Mann-Whitney U test or Student's t-test where appropriate, and categorical data were compared based on the Chi-square test or Fisher's exact test. To calculate the length of various clinical outcomes, including hospital and ICU stay, for deceased patients, the endpoint was specifically defined as the date of death. Multivariable adjusted logistic regression model was used to identify the association of viral sepsis with multiple outcomes. Age, sex, smoking status, body mass index, immunocompromised status, and comorbidities (diabetes, coronary heart diseases, chronic kidney disease) were adjusted in these models. Risk factors for mortality in viral sepsis group were also determined by multivariable adjusted logistic regression. The survival analysis was performed using Kaplan-Meier method and compared using log-rank test. All statistical analyses were performed using IBM SPSS software, version 24.0 (NY, USA) and GraphPad Prism 9.5.1. A two-sided $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

This study enrolled 292 ICU patients with sepsis, comprising 191 cases of viral sepsis and 101 cases of bacterial sepsis (Figure 1). All patients received sputum culture or blood culture tests. Among them, 97.3% (n=284) successfully underwent bronchoscopy with BALF collected for microbiological tests, while 8 patients failed due to rapid death. 245 patients (86.3%) had mNGS tests on BALF for etiological detection. Among the causative pathogens for viral sepsis, SARS-CoV-2 Omicron variant was the most

frequently detected virus (148, 77.5%), followed by influenza virus (27, 14.1%), adenovirus (6, 3.1%), human metapneumovirus (3, 1.6%), and cytomegalovirus (7, 3.7%). Typical bacteria, such as *S. pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, were also identified (supplementary Figure S1). All patients received antibiotic therapy, and a substantial proportion (92%, n = 176) of those diagnosed with viral sepsis received antiviral treatments. The median age of all patients was 67 years and 69% were male. Compared with bacterial sepsis, patients with viral sepsis had statistically significantly higher proportion of overweight (45% vs 24%, $p<0.001$) and use of baseline glucocorticoid (18% vs 8%, $p=0.022$). There were no statistically significant differences in age, sex, smoking status, comorbidities, immunocompromised status, the SOFA and PSI score between two groups (Table 1).

Laboratory tests, treatments, and outcomes

Compared with patients with bacterial sepsis, patients with viral sepsis had statistically significantly lower oxygenation index determined as lower Pao_2/Fio_2 value tested upon ICU admission. Lower absolute helper T lymphocyte counts (CD4, 232 cells/μl vs 393 cells/μl, $p=0.001$) and cytotoxic T lymphocyte counts (CD8, 144 cells/μl vs 176 cells/μl, $p=0.039$), and a higher proportion of lymphocytopenia (71% vs 43%, $p<0.001$) were observed in patients with viral sepsis (Table 2). Besides, patients with viral sepsis showed lower values of procalcitonin, C-reactive protein, and D-dimer.

As shown in Table 3, patients with viral sepsis were identified to receive more treatments of glucocorticoids (including methylprednisolone, prednisone, dexamethasone, and hydrocortisone), intravenous immunoglobulin, and ECMO, and

had a statistically significantly higher proportion of secondary infection (84% vs 39%, p<0.001), ARDS (85% vs 44%, p<0.001), and higher ICU mortality (57% vs 43%, p=0.018). However, a shorter length of ICU stay was also observed (days, 12 vs 15, p=0.003). The survival analysis also showed evidence of the lower survival rate in viral sepsis (Figure 2, log-rank test, p<0.001). No statistically significant difference in terms of other secondary outcomes were found between two groups.

Furthermore, the trajectory of patients that experienced secondary infection and primary outcome was shown in the Sankey diagram (Figure 3). The comparisons of clinical characteristics and outcomes among patients with pure viral sepsis without identified secondary infection (n=30), pure bacterial sepsis (n=62), and viral sepsis with secondary infection (n=161) were shown in supplementary table S1-S3. Compared to patients with pure bacterial sepsis, those with pure viral sepsis had lower mortality despite reaching no statistically significant difference. Almost similar differences were found in comparisons of outcomes between pure viral sepsis and viral sepsis with secondary infection.

Association of primary pathogens with clinical outcomes, risk factors for ICU mortality in viral sepsis

Compared with participants in bacterial sepsis group, the multivariable adjusted odds ratios (ORs, 95% CIs) were 2.26 (1.26-4.07) for ICU mortality, 9.19 (4.92-17.15) for the occurrence of ARDS, and 10.81 (5.78-20.23) for secondary infection in viral sepsis group (Figure 4). Besides, multivariable logistic regression analysis showed that age per ten-year increase (1.37, 95%CI 1.04-1.80), the underlying coronary heart disease

(3.52, 95%CI 1.27-9.73), immunocompromised status (5.29, 95%CI 2.01-13.92), SOFA score (1.34, 95%CI 1.15-1.56), and secondary infection (5.33, 95%CI 1.86-15.24) remained independent risk factors associated with ICU mortality in viral sepsis (Figure 5).

Subgroup analysis

Compared to viral septic patients with only respiratory SOFA subscore, those with at least two organ dysfunction subscores exhibited similar baseline characteristics but a higher ICU mortality (65% vs 11%, $p<0.001$) (supplementary table S4-S6). We further obtained the timeline of clinical outcomes caused by viral sepsis after onset of illness (supplementary Figure S2). The median time from onset of symptoms to the occurrence of sepsis was 9.0 days, to ICU admission was 15.0 days, and to death was 29.0 days. Notably, the secondary infection emerges approximately 9 days after the onset of sepsis. Moreover, the clinical features of among viral septic patients classified by pathogen species were shown in supplementary table S7-S9.

Discussion

In this retrospective observational study, we compared the clinical features and outcomes between patients with viral sepsis and bacterial sepsis. Similar baseline characteristics were found between two groups. More serious primary lung injury indicated by lower oxygen index was determined in viral sepsis cohort. Limited tests of immune function including the number of cytotoxic T cells and helper T cells revealed that more participants with viral sepsis were experiencing worse immune status upon ICU admission. More importantly, viral sepsis patients had worse clinical

outcomes than that in bacterial sepsis. The multivariable adjusted analysis suggested that secondary infection might contribute to the increased ICU mortality in viral sepsis. To our knowledge, this is the first study to compare the clinical features and mortality for viral sepsis versus bacterial sepsis caused by a broad spectrum of causative pathogens confirmed by a comprehensive set of etiological tests, and explore the increased vulnerability and the effect of secondary infection on ICU mortality among viral sepsis patients.

Previous studies have yielded inconsistent results when comparing mortality between viral and bacterial sepsis [7-9, 17]. Ren et al. investigated 21 patients with SARS-CoV-2-induced sepsis and 46 with bacterial sepsis, reporting that patients with bacterial sepsis had more severe organ dysfunction and poor outcomes including higher values in SOFA and APACHE II, as well as more ICU deaths, compared to SARS-CoV-2-induced sepsis [7]. In another study, involving 107 patients with COVID-19 and 63 patients with *carbapenem-resistant klebsiella pneumonia*, it was found that critical COVID-19 shares less severe degree of secondary organ damage and mortality than classical bacterial sepsis [8]. However, Loftus et al. revealed that SARS-CoV-2 patients initially had less severe organ dysfunction but later suffered persistent inflammation and worsen outcomes, especially with secondary bacterial infection [9]. Furthermore, a retrospective cohort study using objective electronic clinical criteria showed that in-hospital mortality rates for SARS-CoV-2–associated sepsis were initially high but gradually declined, ultimately approaching those of presumed bacterial sepsis [17]. Our studies showed that ICU mortality rates were lower in patients with pure viral sepsis

compared to those with pure bacterial sepsis. Conversely, patients with primary viral sepsis who develop secondary infections tend to have worse outcomes than those with bacterial sepsis accompanied by secondary infections. Thus, secondary infection in later stage brings additional risk of disease deterioration and further contributes to poor outcomes in our study. This is consistently elucidated in a study revealing that secondary bacterial infections are independent risk factors for the severity and mortality of COVID-19 [18]. However, previous studies in this field have typically focused on patients with only pure viral or bacterial sepsis [10, 19], which is challenging in ICU that a considerable number of septic patients suffered from secondary infections due to critical care interventions and compromised immune response [19-21]. In addition, our findings revealed that severe sepsis caused by less common respiratory viruses, such as human metapneumovirus, had the potential to result in similar poor outcomes as sepsis caused by SARS-CoV-2 and influenza virus.

The more serious primary lung injury, characterized by decreased oxygen index and increased incidence of ARDS, resulting from viral sepsis in our observation, was consistent with previous findings [7, 8]. Although it is generally assumed that viral sepsis tends to cause milder extrapulmonary organ dysfunction [22], bacterial sepsis, on the other hand, could induce a more serious systemic inflammatory response [23, 24], as evidenced by higher values of procalcitonin and C-reactive protein in current study. However, despite initial differences, both viral and bacterial sepsis eventually manifested similar levels of multi-organ dysfunction at the later phases of sepsis, exhibiting comparable SOFA scores in present study. Moreover, the shorter length of

ICU stay in viral sepsis group may be attributed to delayed ICU admission and a subsequent accelerated clinical deterioration causing death. This underscores the significance of timely interventions, including early antiviral treatment.

Our study offers unique insights into the impact of pathogens and SOFA subscores on sepsis. Notably, previous studies on viral sepsis mostly focused on only one classic pathogen. However, various viruses were expected to converge upon a shared terminal pathway, ultimately leading to analogous diffuse alveolar damage and additional organ damages despite variations in the cytokine profiles elicited by different viruses [25, 26]. Based on this, there have been studies indicating that the severity of pneumonia induced by non-influenza respiratory viruses is comparable to that caused by influenza viruses [12, 27, 28]. McMullen et al. revealed that the composition of the inflammatory infiltrate at the sites of acute lung injury during autopsy did not significantly differ between COVID-19 and influenza cases, highlighting the considerable overlap in nonspecific clinical features and pathological alterations observed among severe cases of COVID-19 and influenza [29]. Zahar et al. also claimed that pathogen species and infection sites are not associated with mortality [30]. Thus, pathogens detected in our study included a broad spectrum of virus and bacteria, rendering a comprehensive understanding of the effects of pathogens on sepsis. In addition, few studies have elucidated the impact of SOFA subscores on clinical characteristics. Our research found evidence that patients with only respiratory SOFA subscore exhibited similar baseline characteristics to those with at least two organ dysfunction subscores. Therefore, both groups were included in our cohort, despite the observed differences in outcomes.

There are a few limitations in current study. First, it was a retrospective study with a small sample size performed in a single center, which limited the precise interpretation of the analysis. However, multiple etiological tests including conventional culture, PCR, and mNGS were conducted in a large percentage of patients in our cohort, rendering an unparalleled advantage in determining the primary and secondary pathogens. Second, the dominant SARS-Cov-2 in viral pathogen limited the extrapolation of concept of respiratory viral sepsis in our study, although we have enrolled all patients who met the inclusion and exclusion criteria. Third, the distinct difference between two groups cannot be extensively applied to septic patients with varying levels of severity, since only septic patients in ICU were included in our cohort.

In conclusion, respiratory virus infection can also lead to sepsis, which can worsen rapidly. Compared to patients with bacterial sepsis, those with respiratory viral sepsis exhibited statistically significantly worse outcomes. The secondary infection, which mostly emerges more than a week following the onset of sepsis, may partially contribute to the increased mortality observed in viral sepsis. More attention is warranted to manage the secondary infections. Future research is necessary to identify more effective biomarkers to facilitate early and adequate treatment for respiratory viral sepsis.

Table 1 Baseline Characteristics of Study Participants

Variable	Total (n=292)	Viral sepsis (n=191)	Bacterial sepsis (n=101)	*P* value
Male	202 (69%)	128 (67%)	74 (73%)	0.271
Age, years	67 (58-75)	68 (60-75)	65 (54-75)	0.159
BMI, kg/m²	23.6 (20.9-26.4)	24.5 (21.5-27.3)	22.1 (20.3-24.9)	<0.001
BMI > 25	109 (37%)	85 (45%)	24 (24%)	<0.001
Smoking status				0.086
Current smoker	48 (16%)	25 (13%)	23 (23%)	
Former smoker	90 (31%)	59 (31%)	31 (31%)	
Never-smoker	154 (53%)	107 (56%)	47 (47%)	
Comorbidity				
Diabetes	119 (41%)	82 (43%)	37 (37%)	0.297
Hypertension	157 (54%)	108 (57%)	49 (49%)	0.191
Malignancy	31 (11%)	16 (8%)	15 (15%)	0.088
Coronary heart diseases	53 (18%)	34 (18%)	19 (19%)	0.831
Cerebrovascular diseases	32 (11%)	17 (9%)	15 (15%)	0.122
Chronic kidney disease	34 (12%)	26 (14%)	8 (8%)	0.149
Connective tissue diseases	27 (9%)	17 (9%)	10 (10%)	0.779
Baseline glucocorticoids	42 (14%)	34 (18%)	8 (8%)	0.022
Immunocompromised status	60 (21%)	43 (23%)	17 (17%)	0.253
Time from symptom onset to hospitalization, days	13 (7-21)	14 (9-21)	11 (5-23)	0.179
Time from symptom onset to ICU admission, days	14 (9-24)	15 (10-24)	12 (6-24)	0.047
SOFA score at ICU admission	7 (5-9)	7 (5-9)	7 (4-9)	0.839
PSI score at ICU admission	136±37	133±35	142±41	0.113

BMI, Body mass index**;** ICU, intensive care unit; PSI, Pneumonia Severity Index; SOFA, Sequential Organ Failure Assessment.

Table 2 Arterial blood gas analysis and laboratory tests at ICU admission

Variable	Total (n=292)	Viral sepsis (n=191)	Bacterial sepsis (n=101)	*P* value
ABG analysis at ICU admission				
Pao_2/Fio_2, mmHg	114 (77-170)	96 (73-154)	141 (97-189)	<0.001
Pao_2/Fio_2 <200	248 (85%)	169 (88%)	79 (78%)	0.020
Pao_2/Fio_2 <100	129 (44%)	102 (53%)	27 (27%)	<0.001
Arterial lactic acid, mmol/L	2.5 (1.9-3.3)	2.6 (2.0-3.3)	2.3 (1.7-3.2)	0.123
CD4, cells/μL	256 (139-460)	232 (130-384)	393 (191-574)	0.001
CD4 < 200	92/245 (38%)	73/172 (42%)	19/73 (26%)	0.015
CD8, cells/μL	154 (76-293)	144 (72-262)	176 (93-424)	0.039
Procalcitonin, ng/ml	0.39 (0.2-1.62)	0.22 (0.20-1.09)	0.80 (0.20-5.90)	0.001
C-reactive protein, mg/L	93 (42-160)	75 (36-147)	136 (75-200)	<0.001
Leukocyte count >10*10⁹/L	153 (52%)	96 (50%)	57 (56%)	0.315
Lymphocytopenia#	178 (61%)	135 (71%)	43 (43%)	<0.001
NLR	13.6 (7.5-28.3)	14.8 (7.8-34.3)	12.0 (7.0-23.4)	0.027
Anemia##	171 (59%)	100 (52%)	71 (70%)	0.003
Platelet, *10⁹/L	181 (118-256)	178 (118-251)	188 (103-268)	0.638
Thrombocytopenia$	108 (37%)	71 (37%)	37 (37%)	0.928
Total bilirubin >20μmol/L	65 (22%)	39 (20%)	26 (26%)	0.298
Albumin <30 g/L	82/227 (36%)	47/148 (32%)	35/79 (44%)	0.061
LDH >250IU/L	186/226 (82%)	129/147 (88%)	57/79 (72%)	0.003
BUN >7 mmol/L	200 (68%)	138 (72%)	62 (61%)	0.057
Creatinine >110 μmol/L	83 (28%)	52 (27%)	31 (31%)	0.532
Na, mmol/L	138 (135-142)	138 (135-142)	138 (134-144)	0.641
Prothrombin Time >15s	113 (39%)	60 (31%)	53 (52%)	<0.001
D-dimer, mg/L	2.8 (1.6-7.5)	2.5 (1.4-7.3)	4.3 (2.2-7.7)	0.009
CKMB, ng/ml	1.8 (1.0-3.6)	1.7 (1.1-3.4)	1.9 (1.0-4.3)	0.348

ABG, Arterial blood gas; BUN, blood urea nitrogen; CD4, helper T lymphocyte; CD8, cytotoxic T lymphocyte; CKMB, creatine kinase isomer-MB; ICU, intensive care unit; LDH, lactic dehydrogenase; NLR, neutrophil-to-lymphocyte ratio.

lymphocyte count < 0.8*10⁹/L; ## haemoglobin <120 g/L for males and <110 g/L for females; $ platelet count <150 *10⁹/L.

Table 3 Treatments and clinical outcomes

Variable	Total (n=292)	Viral sepsis (n=191)	Bacterial sepsis (n=101)	*P* value
Combination antibiotic therapy	194 (66.4%)	123 (64.4%)	71 (70.3%)	0.310
Glucocorticoids treatment	162 (55%)	125 (65%)	37 (37%)	<0.001
IVIG treatment	63 (22%)	49 (26%)	14 (14%)	0.020
Vasoactive agent use	193 (66%)	123 (64%)	70 (69%)	0.399
Secondary infection	200 (68%)	161 (84%)	39 (39%)	<0.001
ARDS	207 (71%)	163 (85%)	44 (44%)	<0.001
Length of ARDS, days	23 (13-33)	22 (14-30)	23 (12-43)	0.397
Septic shock	159 (54%)	100 (52%)	59 (59%)	0.323
Length of Septic shock, days	9 (3-18)	9 (3-17)	11 (4-26)	0.091
AKI	98 (34%)	65 (34%)	33 (33%)	0.815
Length of AKI, days	8 (3-19)	9 (3-19)	14 (5-25)	0.141
HFNC	201 (69%)	137 (72%)	64 (63%)	0.142
Length of HFNC, days	7 (3-12)	6 (3-11)	8 (5-14)	0.048
IMV	225 (77%)	146 (76%)	79 (78%)	0.731
Length of IMV, days	13 (6-26)	12 (6-22)	16 (6-38.5)	0.059
ECMO	38 (13%)	31 (16%)	7 (7%)	0.025
Length of ECMO, days	14 (9-22)	13 (10-21)	14 (11-28)	0.585
CRRT	93 (32%)	67 (35%)	26 (26%)	0.103
Length of CRRT, days	6 (3-19)	6 (3-17)	13 (3-20)	0.077
Length of sepsis, days	23 (13-34)	22 (13-31)	23 (15-38)	0.35
Length of ICU stay, days	13 (7-23)	12 (6-20)	15 (9-30)	0.003
Length of hospital stay, days	20 (12-29)	19 (11-27)	22 (14-33)	0.063
ICU mortality	152 (52%)	109 (57%)	43 (43%)	0.018

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; HFNC, high-flow nasal cannula; ICU, intensive care unit; IMV, invasive mechanical ventilation; IVIG, intravenous immunoglobulin.

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Figure legends

Figure 1. Study flowchart. IMV, invasive mechanical ventilation; CRF, chronic respiratory failure; TB, tuberculosis; HIV, human immunodeficiency virus.

Figure 2. Kaplan–Meier survival curves for 60-day mortality and the overall mortality among viral and bacterial septic patients. ICU, intensive care unit.

Figure 3. Sankey diagram of the trajectory for patients that experienced secondary infection and primary outcome.

Figure 4. Association of primary pathogens detected in septic patients with various outcomes. AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CRRT, continuous renal replacement therapy; ICU, intensive care unit; IMV, invasive mechanical ventilation.

Figure 5. Risk factors for ICU mortality in patients with viral sepsis. BMI, body mass index; SOFA, Sequential Organ Failure Assessment.

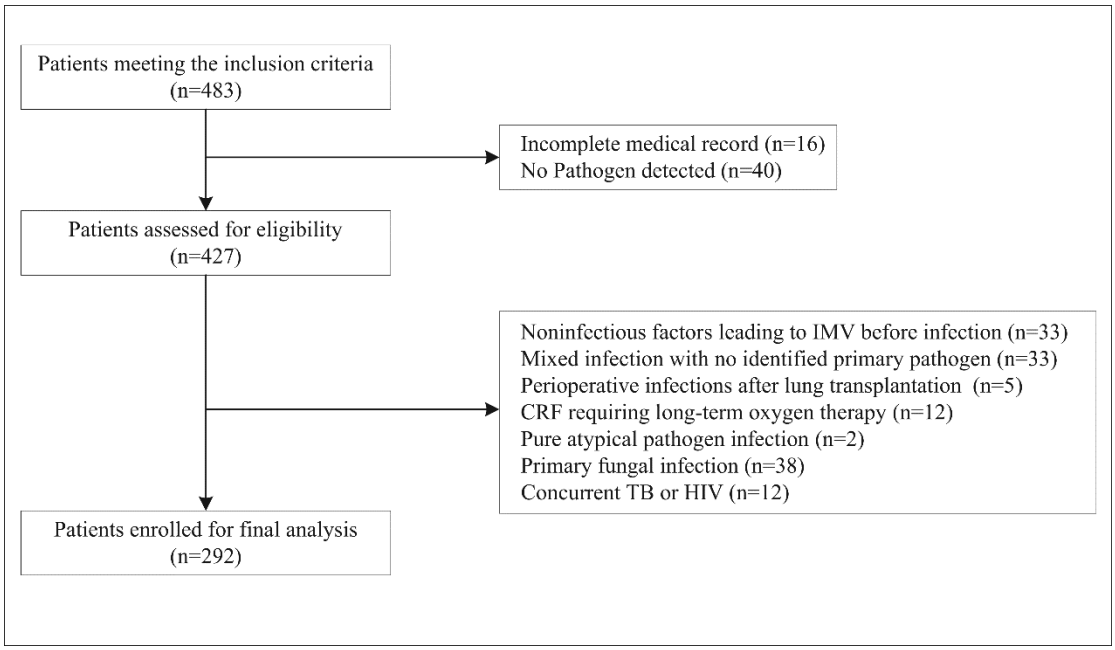

Figure 1

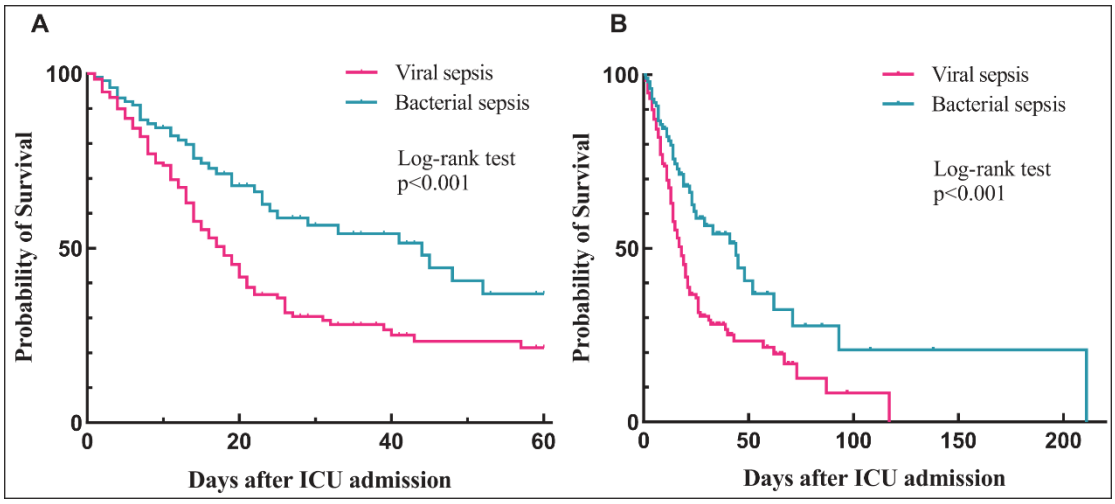

Figure 2

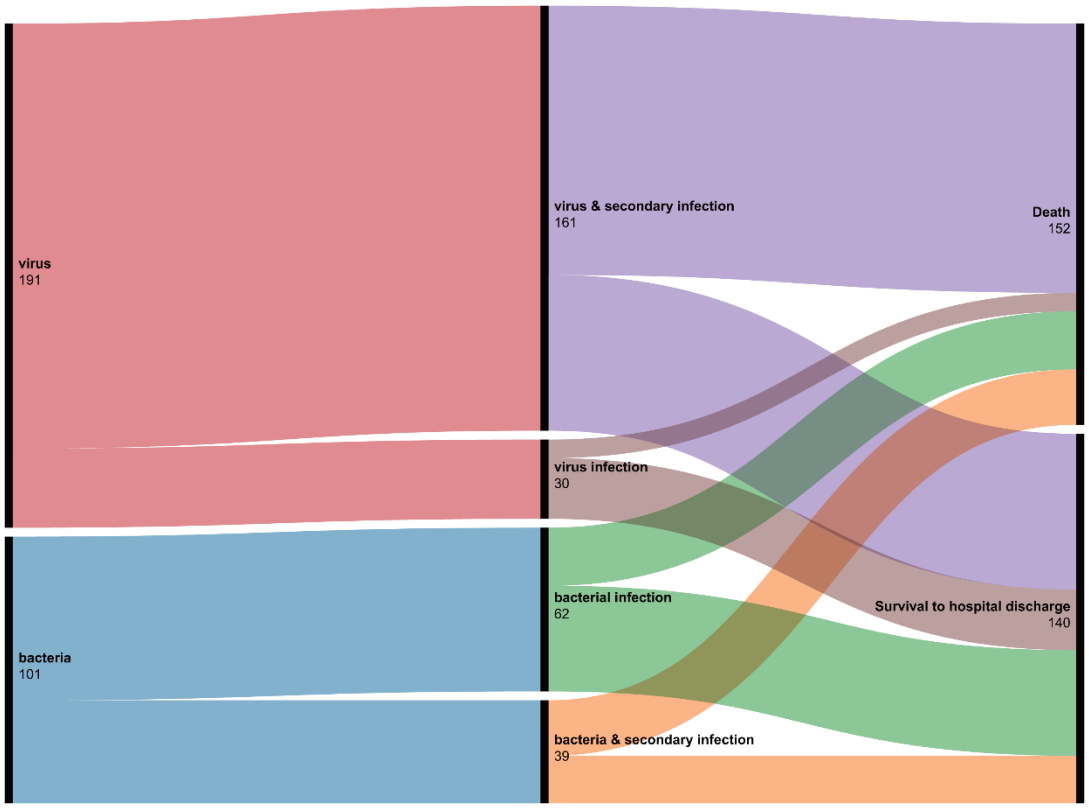

Figure 3

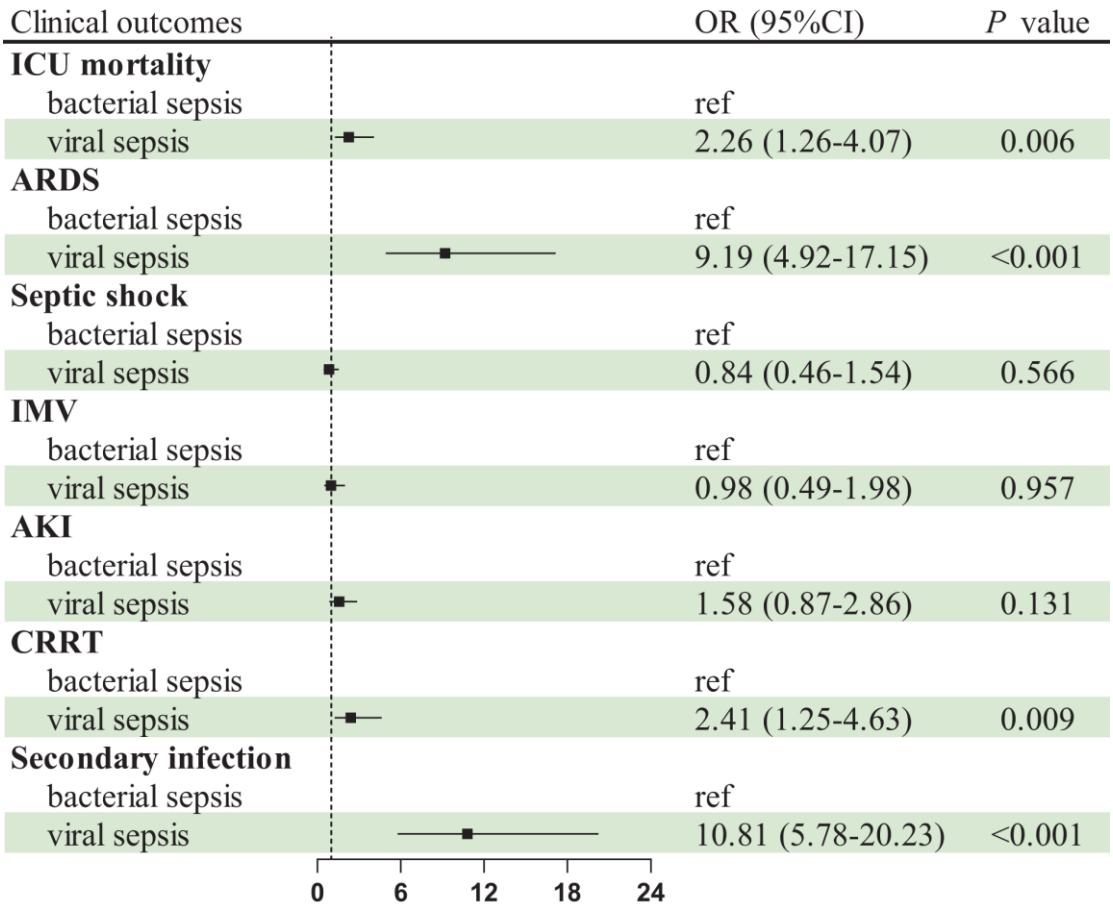

Figure 4

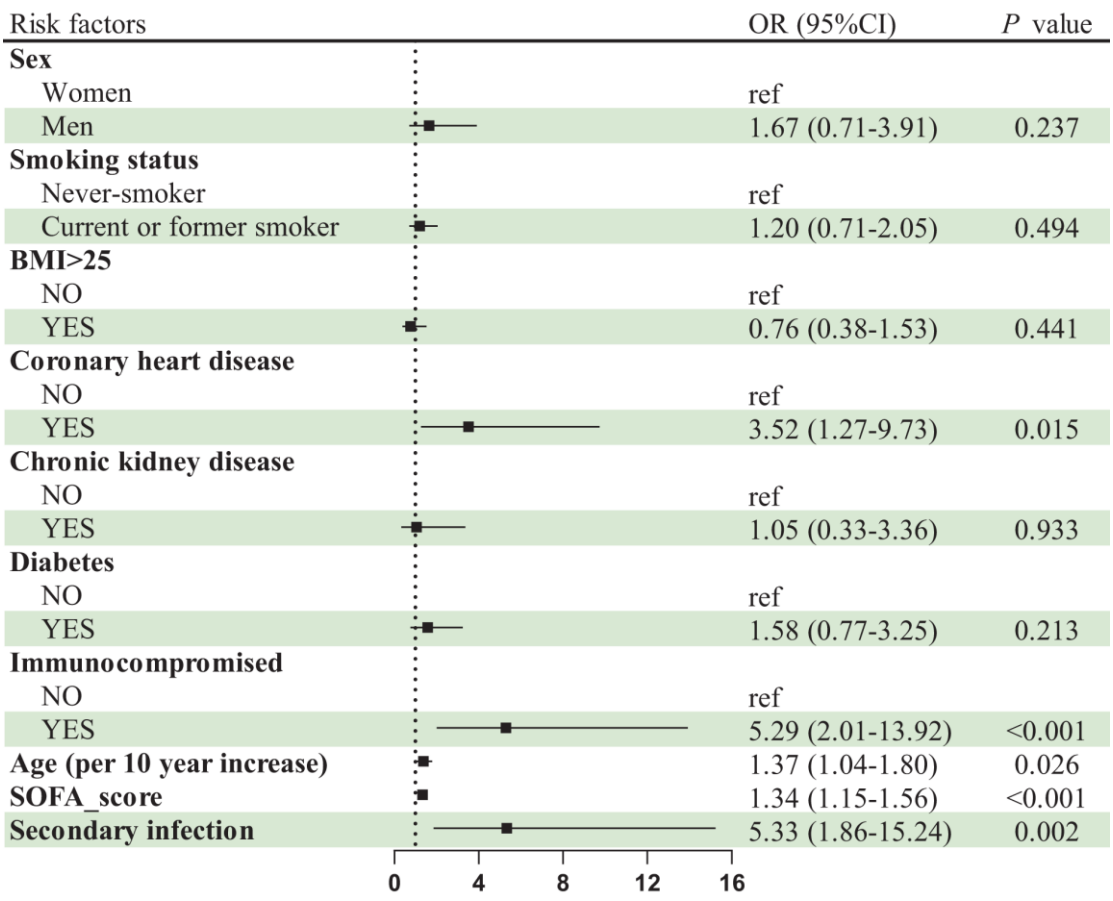

Figure 5

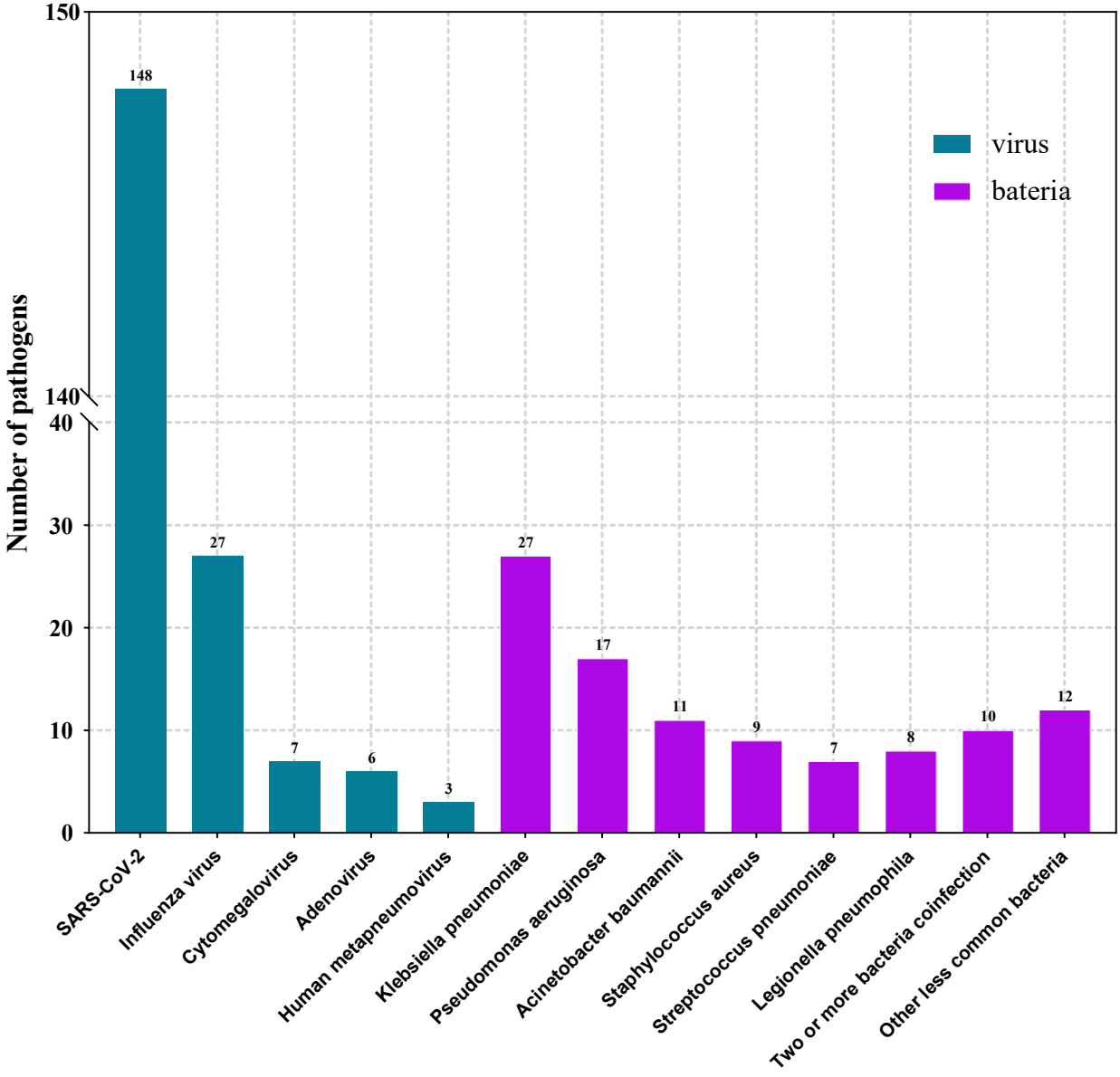

Figure S1. Distribution of the pathogens of primary infection.

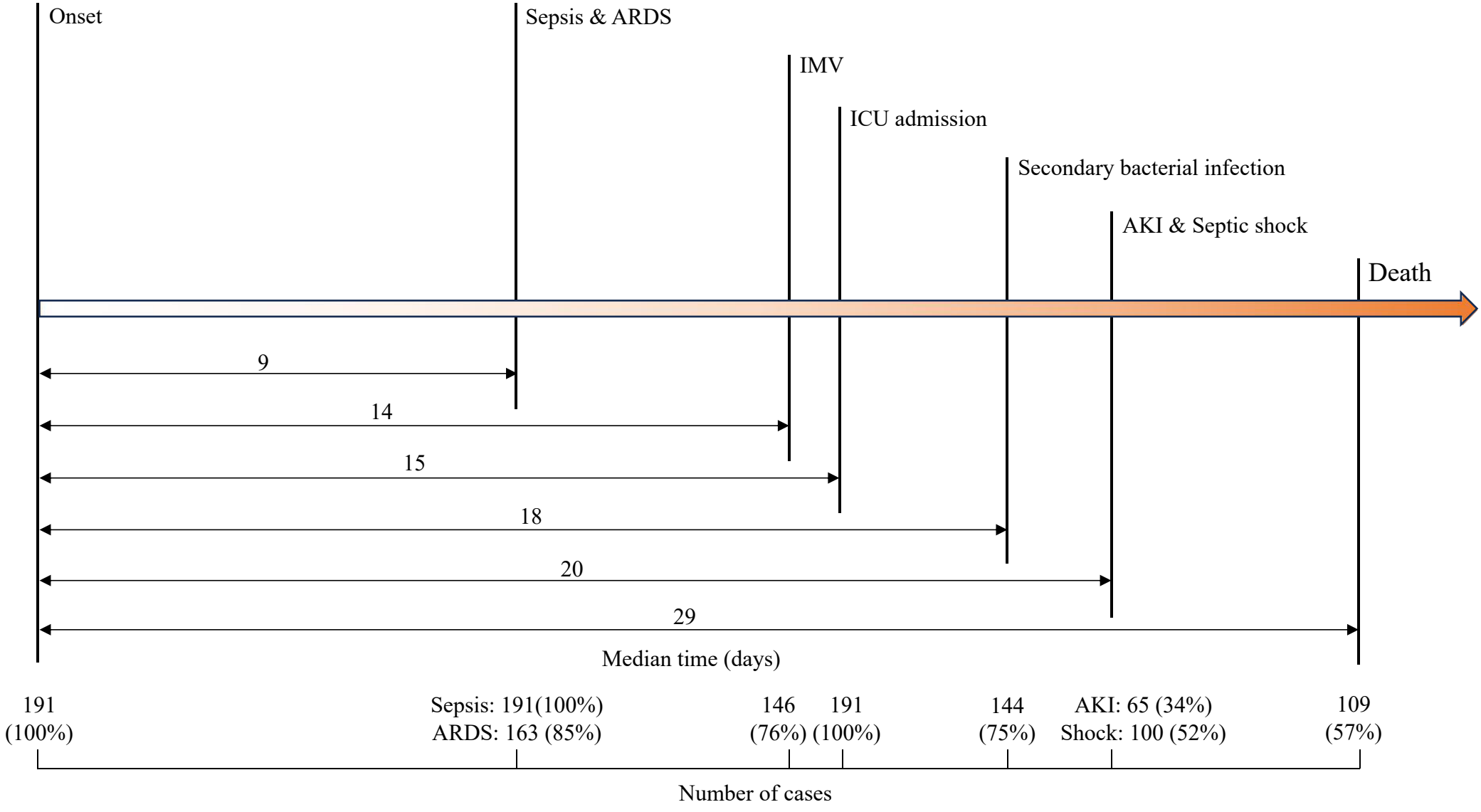

Figure S2. Timeline of clinical outcomes caused by viral sepsis after onset of illness. ARDS, acute respiratory distress syndrome; IMV, invasive mechanical ventilation; AKI, acute kidney injury.

Table S1 Baseline Characteristics of Study Participants

Variable	Pure viral sepsis (n=30)	Pure bacterial sepsis (n=62)	Viral sepsis with secondary infection (n=161)	*P* value Pure Viral vs pure bacterial sepsis	*P* value Pure Viral sepsis vs Viral sepsis with secondary infection
Male	19 (63%)	44 (71%)	109 (68%)	0.460	0.640
Age, years	69 (60-75)	64 (54-76)	68 (60-75)	0.342	0.881
BMI, kg/m²	25.0 (22.2-27.0)	22.5 (20.9-25.6)	24.4 (21.2-27.4)	0.013	0.437
BMI>25	15 (50%)	18 (29%)	70 (43%)	0.049	0.509
Smoking status					
Current smoker	3 (10%)	16 (26%)	22 (14%)	0.188	0.831
Former smoker	9 (30%)	18 (29%)	50 (31%)		
Never-smoker	18 (60%)	28 (45%)	89 (55%)		
Comorbidity					
Diabetes	13 (43%)	23 (37%)	69 (43%)	0.566	0.961
Hypertension	16 (53%)	27 (44%)	92 (57%)	0.378	0.699
Malignancy	2 (7%)	9 (15%)	14 (9%)	0.494	1.000
Coronary heart diseases	4 (13%)	8 (13%)	30 (19%)	1.000	0.486
Cerebrovascular diseases	2 (7%)	8 (13%)	15 (9%)	0.489	1.000
Chronic kidney disease	5 (17%)	4 (6%)	21 (13%)	0.146	0.568
Connective tissue diseases	5 (17%)	4 (6%)	12 (7%)	0.146	0.153
Baseline steroids	4 (13%)	4 (6%)	30 (19%)	0.430	0.486
Immunocompromised status	7 (23%)	8 (13%)	36 (22%)	0.236	0.907
Time from symptom onset to hospitalization, days	15 (10-25)	10 (5-20)	14 (9-21)	0.058	0.644
SOFA score at ICU admission	5 (3-7)	7 (4-10)	7 (5-9)	0.020	<0.001
PSI score at ICU admission	112 (95-129)	134 (112-161)	136 (113-158)	0.001	<0.001

BMI, Body mass index**;** ICU, intensive care unit; PSI, Pneumonia Severity Index; SOFA, Sequential Organ Failure Assessment.

Table S2 Arterial blood gas analysis and laboratory tests at ICU admission

Variable	Pure Viral sepsis (n=30)	Pure Bacterial sepsis (n=62)	Viral sepsis with secondary infection (n=161)	*P* value Pure Viral vs pure bacterial sepsis	*P* value Pure Viral sepsis vs Viral sepsis with secondary infection
ABG analysis at hospital admission					
Pao_2/Fio_2, mmHg	133 (85-160)	140 (104-211)	111 (78-164)	0.181	0.521
Pao_2/Fio_2 <200	27 (90%)	44 (71%)	133 (83%)	0.041	0.423
Pao_2/Fio_2 <100	9 (30%)	14 (23%)	76 (47%)	0.441	0.082
Arterial lactic acid, mmol/L	2.2 (1.6-2.6)	2.1 (1.4-2.7)	2.4 (1.8-3.2)	0.877	0.184
ABG analysis at ICU admission					
Pao_2/Fio_2, mmHg	133 (80-160)	137 (97-196)	95 (70-146)	0.304	0.085
Pao_2/Fio_2 <200	27 (90%)	47 (76%)	142 (88%)	0.108	1.000
Pao_2/Fio_2 <100	9 (30%)	16 (26%)	93 (58%)	0.672	0.005
Arterial lactic acid, mmol/L	2.3 (1.4-2.7)	2.3 (1.6-3.4)	2.7 (2.0-3.3)	0.438	0.014
ABG analysis at sepsis onset					
Pao_2/Fio_2, mmHg	178 (118-228)	162 (120-207)	153 (105-189)	0.476	0.098
Pao_2/Fio_2 <200	16/27 (59%)	41/57 (72%)	121/153 (79%)	0.246	0.026
Pao_2/Fio_2 <100	6/27 (22%)	10/57 (18%)	34/153 (22%)	0.610	1.000
Arterial lactic acid, mmol/L	1.6 (1.3-2.2)	1.8 (1.2-2.4)	1.5 (1.2-2.2)	0.705	0.742
Laboratory tests at ICU admission					
CD4, cells/µL	347 (151-532)	328 (170-618)	214 (131-345)	0.686	0.072
CD4 < 100	4/27 (15%)	7/39 (18%)	28/145 (19%)	1.000	0.582
CD4 < 200	9/27 (33%)	11/39 (28%)	64/145 (44%)	0.656	0.297
CD8, cells/µL	184 (114-278)	130 (59-292)	136 (65-260)	0.265	0.149

ABG, Arterial blood gas; CD4, helper T lymphocyte; CD8, cytotoxic T lymphocyte; ICU, intensive care unit.

Table S3 Treatments and clinical outcomes

Variable	Pure Viral sepsis (n=30)	Pure Bacterial sepsis (n=62)	Viral sepsis with secondary infection (n=161)	*P* value Pure Viral vs pure bacterial sepsis	*P* value Pure Viral sepsis vs Viral sepsis with secondary infection
Glucocorticoids treatment	19 (63%)	18 (29%)	106 (66%)	0.002	0.791
IVIG treatment	3 (10%)	5 (8%)	46 (29%)	0.713	0.032
Vasoactive agent use	9 (30%)	38 (61%)	114 (71%)	0.005	<0.001
ARDS	22 (73%)	24 (39%)	141 (86%)	0.002	0.052
Length of ARDS, days	20 (12-27)	16 (11-33)	22 (14-31)	0.886	0.331
Septic shock	5 (17%)	32 (52%)	95 (59%)	0.001	<0.001
Length of Septic shock, days	11 (2-13)	8 (3-18)	6 (2-16)	0.704	0.994
AKI	3 (10%)	21 (34%)	62 (39%)	0.015	0.002
Length of AKI, days	8 (5-12)	11 (3-18)	6 (3-18)	0.662	0.888
HFNC	26 (87%)	36 (58%)	111 (69%)	0.006	0.048
Length of HFNC, days	11 (5-19)	8 (5-12)	5 (3-9)	0.238	0.005
IMV	7 (23%)	46 (74%)	139 (86%)	<0.001	<0.001
Length of IMV, days	8 (4-11)	12 (5-26)	13 (6-22)	0.189	0.084
ECMO	1 (3%)	2 (3%)	30 (19%)	1.000	0.055
CRRT	4 (13%)	14 (23%)	63 (39%)	0.295	0.007
Length of CRRT, days	15 (7-23)	8 (3-17)	5 (3-16)	0.669	0.402
Length of sepsis, days	21 (12-27)	18 (11-30)	23 (14-33)	0.957	0.218
Length of ICU stay, days	8 (6-12)	14 (7-24)	13 (7-21)	0.007	0.010
Length of hospital stay, days	18 (10-21)	19 (12-28)	19 (11-29)	0.257	0.199
ICU mortality	7 (23%)	22 (35%)	102 (63%)	0.240	<0.001

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; HFNC, high-flow nasal cannula; ICU, intensive care unit; IMV, invasive mechanical ventilation; IVIG, intravenous immunoglobulin.

Table S4 Baseline Characteristics of Study Participants

Variable	Viral sepsis with only respiratory SOFA subscore (n=28)	Viral sepsis with ≥2 organ dysfunction subscores (n=163)	*P* value
Male	13 (46%)	115 (71%)	0.012
Age, years	70 (59-73)	68 (60-76)	0.657
BMI, kg/m^2	24.7 (22.0-26.9)	24.2 (21.3-27.4)	0.846
BMI>25	13 (46%)	72 (44%)	0.824
Smoking status			
Current smoker	3 (11%)	22 (13%)	0.634
Former smoker	7 (25%)	52 (32%)	
Never-smoker	18 (64%)	89 (55%)	
Comorbidity			
Diabetes	10 (36%)	72 (44%)	0.404
Hypertension	16 (57%)	92 (56%)	0.945
Malignancy	3 (11%)	13 (8%)	0.710
Coronary heart diseases	5 (18%)	29 (18%)	1.000
Cerebrovascular diseases	4 (14%)	13 (8%)	0.283
Chronic kidney disease	1 (4%)	25 (15%)	0.134
Connective tissue diseases	4 (14%)	13 (8%)	0.283
Baseline glucocorticoids	4 (14%)	30 (18%)	0.791
Immunocompromised status	5 (18%)	38 (23%)	0.523
Time from symptom onset to hospitalization, days	17 (12-27)	14 (9-21)	0.060
SOFA score at ICU admission	3 (3-4)	7 (6-9)	<0.001
PSI score at ICU admission	102 (91-130)	135 (114-158)	<0.001

BMI, Body mass index**;** ICU, intensive care unit; PSI, Pneumonia Severity Index; SOFA, Sequential Organ Failure Assessment.

Table S5 Arterial blood gas analysis and laboratory tests at ICU admission

Variable	Viral sepsis with only respiratory SOFA subscore (n=28)	Viral sepsis with ≥2 organ dysfunction subscores (n=163)	*P* value
ABG analysis at hospital admission			
Pao_2/Fio_2, mmHg	161 (100-202)	106 (76-160)	0.004
Pao_2/Fio_2 <200	21 (75%)	139 (85%)	0.174
Pao_2/Fio_2 <100	7 (25%)	78 (48%)	0.025
Arterial lactic acid, mmol/L	2.0 (1.4-2.6)	2.4 (1.8-3.2)	0.004
ABG analysis at ICU admission			
Pao_2/Fio_2, mmHg	155 (95-188)	94 (69-140)	<0.001
Pao_2/Fio_2 <200	22 (79%)	147 (90%)	0.103
Pao_2/Fio_2 <100	8 (29%)	94 (58%)	0.004
Arterial lactic acid, mmol/L	2.0 (1.4-2.6)	2.7 (2.0-3.3)	<0.001
ABG analysis at sepsis onset			
Pao_2/Fio_2, mmHg	165 (150-212)	145 (95-189)	0.018
Pao_2/Fio_2 <200	17/27 (63%)	120/153 (78%)	0.082
Pao_2/Fio_2 <100	1/27 (4%)	39/153 (25%)	0.012
Arterial lactic acid, mmol/L	1.5 (1.2-2.0)	1.6 (1.2-2.2)	0.601
Laboratory tests at ICU admission			
CD4, cells/μL	303 (167-467)	212 (127-373)	0.095
CD4 < 100	3/26 (12%)	29/146 (20%)	0.418
CD4 < 200	8/26 (31%)	65/146 (45%)	0.191
CD8, cells/μL	197 (95-367)	134 (65-239)	0.052

ABG, Arterial blood gas; CD4, helper T lymphocyte; CD8, cytotoxic T lymphocyte; ICU, intensive care unit.

Table S6. Treatments and clinical outcomes

Variable	Viral sepsis with only respiratory SOFA subscore (n=28)	Viral sepsis with ≥2 organ dysfunction subscores (n=163)	*P* value
Glucocorticoids treatment	18 (64%)	107 (66%)	0.889
IVIG treatment	3 (11%)	46 (28%)	0.050
Vasoactive agent use	4 (14%)	119 (73%)	<0.001
ARDS	21 (75%)	142 (87%)	0.142
Length of ARDS, days	25 (16-31)	21 (13-29)	0.210
Septic shock	4 (14%)	96 (59%)	<0.001
Length of Septic shock, days	7 (2-24)	6 (2-16)	1.000
AKI	1 (4%)	64 (39%)	<0.001
HFNC	27 (96%)	110 (67%)	0.002
Length of HFNC, days	9 (5-20)	5 (3-10)	0.002
IMV	8 (29%)	138 (85%)	<0.001
Length of IMV, days	11 (8-34)	13 (5-22)	0.767
ECMO	1 (4%)	30 (18%)	0.053
CRRT	2 (7%)	65 (40%)	0.001
Length of CRRT, days	7 (6-8)	5 (3-17)	0.767
Length of sepsis, days	24 (14-33)	22 (13-31)	0.560
Length of ICU stay, days	10 (6-18)	12 (7-20)	0.349
Length of hospital stay, days	20 (16-27)	18 (10-28)	0.178
ICU mortality	3 (11%)	106 (65%)	<0.001

ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; HFNC, high-flow nasal cannula; ICU, intensive care unit; IMV, invasive mechanical ventilation; IVIG, intravenous immunoglobulin; SOFA, Sequential Organ Failure Assessment.

Table S7 Baseline Characteristics of Study Participants

Variable	SARS-CoV-2 associated sepsis (n=148)	Influenza associated sepsis (n=27)	Adenovirus associated sepsis (n=6)	HMPV associated sepsis (n=3)	CMV associated sepsis (n=7)
Male	103 (70%)	14 (52%)	5 (83%)	2 (67%)	4 (57%)
Age, years	70 (63-76)	62 (42-69)	42 (39-55)	57 (39-64)	59 (57-66)
BMI, kg/m^2	24.8 (22.0-27.3)	21.9 (19.6-27.5)	29.3 (19.5-38.3)	26.8 (23.1-30.3)	21.5 (20.2-23.5)
BMI>25	68 (46%)	11 (41%)	3 (50%)	2 (67%)	1 (14%)
Smoking status					
Current smoker	15 (10%)	6 (22%)	4 (67%)	0	0
Former smoker	49 (33%)	5 (19%)	0	1 (33%)	4 (57%)
Never-smoker	84 (%)	16 (59%)	2 (33%)	2 (67%)	3 (43%)
Comorbidity					
Diabetes	64 (57%)	13 (48%)	3 (50%)	1 (33%)	1 (14%)
Hypertension	91 (61%)	10 (37%)	3 (50%)	2 (67%)	2 (29%)
Malignancy	14 (9%)	0	0	1 (33%)	1 (14%)
Coronary heart diseases	32 (22%)	0	2 (33%)	0	0
Cerebrovascular diseases	15 (10%)	1 (4%)	0	1 (33%)	0
Chronic kidney disease	19 (13%)	3 (11%)	2 (33%)	1 (33%)	1 (14%)
Connective tissue diseases	11 (7%)	0	1 (17%)	0	5 (71%)
Baseline glucocorticoids	24 (16%)	4 (15%)	1 (17%)	0	5 (71%)
Immunocompromised status	33 (22%)	3 (11%)	1 (17%)	0	6 (86%)
Time from symptom onset to hospitalization, days	15 (10-23)	8 (6-14)	10 (9-15)	7 (6-9)	12 (7-22)
SOFA score at ICU admission	7 (5-9)	7 (5-10)	7 (6-12)	6 (5-8)	8 (6-9)
PSI score at ICU admission	132 (110-158)	133 (101-151)	104 (88-141)	121 (111-139)	118 (87-132)

BMI, Body mass index; CMV, cytomegalovirus; HMPV, human metapneumovirus; ICU, intensive care unit; PSI, Pneumonia Severity Index; SOFA, Sequential Organ Failure Assessment.

Table S8 Arterial blood gas analysis and laboratory tests at ICU admission

Variable	SARS-CoV-2 associated sepsis (n=148)	Influenza associated sepsis (n=27)	Adenovirus associated sepsis (n=6)	HMPV associated sepsis (n=3)	CMV associated sepsis (n=7)
ABG analysis at hospital admission					
Pao_2/Fio_2, mmHg	101 (76-163)	137 (96-164)	121 (106-269)	133 (124-138)	138 (102-210)
Pao_2/Fio_2 <200	125 (84%)	24 (89%)	4 (67%)	3 (100%)	4 (57%)
Pao_2/Fio_2 <100	74 (50%)	8 (30%)	1 (17%)	0	2 (29%)
Arterial lactic acid, mmol/L	2.5 (1.8-3.2)	2.2 (1.4-3.3)	2.0 (1.5-2.3)	1.9 (1.7-2.9)	2.1 (1.7-2.5)
ABG analysis at ICU admission					
Pao_2/Fio_2, mmHg	90 (69-146)	137 (93-164)	107 (78-134)	133 (124-138)	96 (77-159)
Pao_2/Fio_2 <200	132 (89%)	24 (89%)	5 (83%)	3 (100%)	5 (71%)
Pao_2/Fio_2 <100	87 (59%)	9 (33%)	2 (33%)	0	4 (57%)
Arterial lactic acid, mmol/L	2.7 (2.0-3.3)	2.3 (1.4-3.3)	2.0 (1.4-2.3)	1.9 (1.7-2.9)	2.4 (2.2-3.0)
ABG analysis at sepsis onset					
Pao_2/Fio_2, mmHg	142 (98-193)	162 (153-206)	183 (92-252)	178 (135-214)	185 (158-200)
Pao_2/Fio_2 <200	110/140 (79%)	17/25 (68%)	3/5 (60%)	2/3 (67%)	5/7 (71%)
Pao_2/Fio_2 <100	35/140 (25%)	2/25 (8%)	2/5 (40%)	1/3 (33%)	0
Arterial lactic acid, mmol/L	1.5 (1.2-2.1)	2.4 (1.5-4.0)	1.5 (1.5-1.6)	1.8 (1.4-2.4)	1.5 (1.2-1.8)
Laboratory tests at ICU admission					
CD4, cells/μL	209 (119-332)	379 (181-618)	256 (184-508)	652 (545-705)	303 (178-541)
CD4 < 100	27/136 (20%)	4/22 (18%)	1/5 (20%)	0	0
CD4 < 200	63/136 (46%)	6/22 (27%)	2/5 (40%)	0	2/6 (33%)
CD8, cells/μL	121 (68-224)	199 (131-303)	150 (51-227)	334 (287-343)	429 (286-441)

ABG, Arterial blood gas; CD4, helper T lymphocyte; CD8, cytotoxic T lymphocyte; CMV, cytomegalovirus; HMPV, human metapneumovirus; ICU, intensive care unit.

Table S9 Treatments and clinical outcomes

Variable	SARS-CoV-2 associated sepsis (n=148)	Influenza associated sepsis (n=27)	Adenovirus associated sepsis (n=6)	HMPV associated sepsis (n=3)	CMV associated sepsis (n=7)
Glucocorticoids treatment	107 (72%)	9 (33%)	2 (33%)	0	7 (100%)
IVIG treatment	39 (26%)	5 (19%)	1 (17%)	1 (33%)	3 (43%)
Vasoactive agent use	100 (68%)	14 (52%)	3 (50%)	2 (67%)	4 (57%)
ARDS	129 (87%)	21 (78%)	6 (100%)	2 (67%)	5 (71%)
Septic shock	83 (56%)	11 (41%)	1 (17%)	2 (67%)	3 (43%)
AKI	52 (35%)	10 (37%)	2 (33%)	1 (33%)	0
HFNC	104 (70%)	22 (81%)	4 (67%)	3 (100%)	4 (57%)
IMV	114 (77%)	22 (81%)	4 (67%)	1 (33%)	5 (71%)
ECMO	22 (15%)	4 (15%)	3 (50%)	0	2 (29%)
CRRT	54 (36%)	7 (26%)	3 (50%)	1 (11%)	2 (29%)
Length of sepsis, days	22 (14-33)	23 (13-30)	24 (13-27)	22 (14-30)	22 (12-24)
Length of ICU stay, days	11 (6-19)	16 (8-29)	15 (8-38)	14 (10-25)	8 (6-15)
Length of hospital stay, days	18 (11-27)	22 (14-32)	20 (12-23)	21 (15-28)	16 (8-20)
ICU mortality	92 (62%)	9 (33%)	2 (33%)	0	6 (86%)

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CMV, cytomegalovirus; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; HFNC, high-flow nasal cannula; HMPV, human metapneumovirus; ICU, intensive care unit; IMV, invasive mechanical ventilation; IVIG, intravenous immunoglobulin.